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Program Release Date: September 2003 Program Expiration Date: September 30, 2004

ACHIEVING REMISSION IN DEPRESSION: Managing Women and Men in the Primary Care Setting

PRESENTED BY:

The Office on Women's Health
of the
US Department of Health and Human Services

IN COOPERATION WITH:

American Medical Association
Physicians dedicated to the health of America

American Psychiatric Association

American College of Physicians

American Academy of Physician Assistants

National Association of Managed Care Physicians

Society for Women's Health Research

This program is supported through an unrestricted educational grant provided by Wyeth.

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September 2003

Dear Colleague,

We are pleased to provide you with this continuing medical education newsletter, *Achieving Remission in Depression: Managing Women and Men in the Primary Care Setting,* developed from the proceedings of a roundtable meeting presented by the Office on Women's Health of the US Department of Health and Human Services.

Depression is a greatly underdiagnosed and undertreated disorder that has significant economic and personal costs for patients and for our society at large. Unrecognized depression can result in morbidity and mortality; however, appropriate early diagnosis and treatment can significantly reduce these risks. Primary care physicians (PCPs) are often the first medical contact that patients suffering from depression encounter. Therefore, it is vital that PCPs are able to identify and treat the disease effectively. Achieving and maintaining remission in depression is the ultimate goal for PCPs and their patients and is specifically addressed in this educational program.

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We thank you in advance for your participation and believe that you will find this newsletter to be an invaluable resource in the management of depression to achieve and maintain remission.

Best regards,

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ACHIEVING REMISSION IN DEPRESSION: Managing Women and Men in the Primary Care Setting

Presented by The Office on Women's Health of the US Department of Health and Human Services

DEPRESSION — A MAJOR PUBLIC HEALTH CONCERN

Depression is an important public health problem with an estimated annual cost of $44 billion.[1] It is currently ranked by the World Health Organization as the fourth most disabling illness and is projected to be the second by the year 2010.[2] Depression is both underdiagnosed and undertreated. Treatment may be lifelong for many patients once the diagnosis is made.[3-5] The personal price of depression includes not only mental anguish but also impaired family and social functioning, impaired work performance, increased morbidity from comorbid medical conditions, suicide (10% to 15% in patients with major depressive disorder), and other mortality risks.[3,4,6] With appropriate treatment, however, up to 80% to 90% of patients can be treated successfully.[3,4,6]

Primary care physicians play a key role in the provision of mental health services—both in terms of identifying patients in need of mental health services and in managing these patients and their needs.

EDUCATIONAL OBJECTIVES

Upon completion of this program, participants should be able to:

- Identify differences in the evaluation and treatment of depression by gender and across the female reproductive cycle
- Differentiate remission and response as goals of the treatment of depression
- Discuss strategies to achieve and maintain remission long term in patients with depression
- Discuss measures to evaluate remission and response to treatment
- Discuss differences among antidepressant classes with respect to safety and efficacy in women and men

TARGET AUDIENCE

Primary care physicians and healthcare professionals who care for patients with depression.

Table 1

Treatment Outcomes in Depression[4,9]

• Response	Clinically significant reduction in baseline symptom severity
• Remission	Absence of symptoms; return of premorbid psychosocial functioning; no longer meets criteria for major depression
• Relapse	Return of depressive symptoms within 6 months following remission
• Recovery	Sustained period of remission of at least 6 months following an episode of major depression
• Recurrence	New episode of depression following recovery from previous episode

They provide a larger proportion of mental health services than do specialists in mental and addictive disorders.[7] Approximately 30% of patients seen in primary care settings present with symptoms of a mental or addictive disorder, with symptoms of depression occurring in 10% to 21% of patients.[3,7,8] Many patients, therefore, rely on their primary care physician to make an accurate diagnosis and prescribe effective treatment for their symptoms of depression. An estimated 50% of antidepressant prescriptions are written by primary care physicians, an indication that primary care physicians are responding to the challenge.

"Depression should be seen as another chronic medical illness with all of the nuances of treating a chronic medical illness."
M.H. Trivedi, MD

Treatment outcomes in depression are defined in Table 1.[4,9] It is only in the last 5 to 10 years that the psychiatric community has moved the treatment paradigm for depression from symptom relief/response to

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one of treating to remission. Treating to remission, ie, achieving a virtually asymptomatic state, rather than response is now the ultimate goal of antidepressant therapy. Increasing evidence indicates that depression is not an episodic disease; rather, it is a chronic and recurrent illness. These shifts in concepts about depression necessitate a change in approach to its treatment and evaluation: primary care physicians need to approach the treatment of depression as they do other chronic medical illnesses. A recent meta-analysis of 31 randomized trials demonstrated a 70% reduction in the odds of relapse of depression with continued treatment versus treatment discontinuation,[10] which underscores the feasibility of both achieving and maintaining remission with treatment.

GENDER DIFFERENCES IN DEPRESSION

"A patient's gender, and for women, their menopausal status, should be considered in both the evaluation and treatment of depression."
S.G. Kornstein, MD

An outgrowth of the women's health movement is the recent recognition of gender differences in the prevalence, presentation, and treatment of psychiatric illnesses, including depression. Epidemiologic data indicate that the prevalence of major depression in women is about two times higher than in men; this difference begins in early adolescence and persists through the mid-50s, corresponding roughly to the reproductive years of women.[11] Biologic and psychosocial factors may contribute to the difference in prevalence, which is consistent across studies in both community samples and clinical trial settings.[12] Gender differences in the clinical features of depression include more atypical symptoms, anxiety, and eating disorders in women, whereas men have an increased risk of completed suicide and are more likely to have comorbid alcohol and substance abuse (Table 2).[12,13] Women may have longer episodes of depression and more chronic or recurrent illness, and hormonal triggers, stressful life events, and seasonal changes are common precipitating factors.

Gender differences also have been shown in response to treatment of depression (Table 3, page 4).[14-17] Women may respond better to selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) than to tricyclic antidepressants (TCAs). Both women and men can be successfully treated to remission with appropriate therapy, with higher remission rates reported in both women and men treated with a serotonin–norepinephrine reuptake inhibitor (SNRI) like venlafaxine compared with an SSRI.[13-18] Gender differences in response to psychotherapy are less apparent, although some differences by gender and age in response to psychotherapy with/without pharmacotherapy have been shown.[16,17] For example, response to combined treatment with psychotherapy plus tricyclics was greater than the response to psychotherapy alone in

Table 2

Gender Differences in Clinical Features and Response to Treatment of Depression[12,13]

• Symptoms	Atypical symptoms more common in women Completed suicide risk increased in men
• Course	Episodes may be longer in women Depression may be more chronic and recurrent in women
• Comorbidity	Anxiety and eating disorders in women Alcohol and substance abuse in men
• Precipitating factors in women	Stressful life events Seasonal changes Reproductive events

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The program consists of a 16-page *Clinical Courier*® with a CME Post-test.

This *Clinical Courier* should take approximately 2 hours to complete. The participant should, in order, review the educational objectives, read the newsletter, and return the completed Post-test and Evaluation Form to the address indicated to receive credit. The Evaluation Form provides each participant with the opportunity to comment on the extent to which educational objectives were met, the quality of the instructional process, the perception of enhanced professional effectiveness, the perception of commercial bias, and participant views on future educational needs. This credit is valid through September 30, 2004. No credit will be given after this date.

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Achieving Remission in Depression: Managing Women and Men in the Primary Care Setting, as published in this issue of the *Clinical Courier*, reports highlights from a meeting of experts in treating depression held in Washington, DC, on March 17, 2003. This publication is intended for healthcare professionals who care for patients with depression. This newsletter was developed and produced by SynerMed Communications under an unrestricted educational grant from Wyeth.

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men and older women, but not in younger women.[17] The data regarding gender differences are preliminary in that they are based primarily on post hoc analyses of studies underpowered to demonstrate gender differences. Nonetheless, clinicians need to consider gender in their evaluation and treatment of patients with depression.

DEPRESSION ACROSS THE FEMALE LIFE CYCLE

There are critical periods in the reproductive lives of women that require special consideration regarding the treatment of depression. Several factors, including physiologic and psychosocial factors and psychiatric history, contribute to the increased risk of depression and relapse as well as to the likelihood of achieving remission in women.

Premenstrual Phase

The premenstrual phase of the menstrual cycle is associated with increased vulnerability for the onset of an episode of depression or worsening of ongoing depression, as well as increased psychiatric hospital admissions and suicide attempts.[19] Approximately 40% to 60% of women with a chief complaint of premenstrual syndrome (PMS) have an underlying mood or anxiety disorder.[19,20] Women who suffer from moderate to severe symptoms of premenstrual depressed mood, anxiety, irritability, and mood swings as part of premenstrual dysphoric disorder (PMDD) experience relatively high levels of impairment that are nearly comparable to levels observed in major depression.[21] Although a number of treatments have been studied for PMS and PMDD, antidepressants, specifically SSRIs and the SNRI venlafaxine, show consistent improvement in both mood and physical symptoms beginning in the first cycle.[21-23] Several studies indicate that intermittent treatment (day 14 or 15 through first day of menses) with an antidepressant is effective treatment for PMDD.[24-27]

Pregnancy and Postpartum Periods

"Treatment decisions in women who are pregnant or breast-feeding are based on risk/benefit assessments of the impact of prenatal or neonatal exposure to psychiatric medications and the impact of untreated psychiatric disorders on the fetus or newborn."
L.S. Cohen, MD

There is a growing consensus that pregnancy does not protect against mood and anxiety disorders or other types of psychiatric illness.[28,29] It is necessary, therefore, to have strategies for treating women who become pregnant and have been on maintenance therapy for mood disorders or who develop symptoms during pregnancy. Because of a general recommendation to avoid prenatal exposure to psychiatric medications when possible and the recognition that untreated psychiatric illness can adversely affect fetal outcome, the decision is based on the risk/benefit to mother and fetus with the understanding that no decision is risk-free. A growing body of evidence indicates that SSRIs and SNRIs do not adversely affect pregnancy outcome or the risk of teratogenesis.[30-33] All antidepressants are found in breast milk in varying concentrations, and the milk:plasma ratio is a poor indicator of fetal exposure.[34] No antidepressant is contraindicated or safer than another during the postpartum period; thus, their use is based on risk/benefit assessments.[34,35] A useful resource for assistance in risk/benefit decisions during pregnancy and postpartum is the website of the Massachusetts General Hospital's Center for Women's Mental Health: http://www.womensmentalhealth.org.

Depression prior to or during pregnancy is the strongest predictor of postpartum depression (PPD), with another strong risk factor being a history of psychiatric disorder.[35] The prevalence of PPD is 5% to 10%, which is equivalent to the prevalence of depression in nonpuerperal, age-matched women.[28] Although the majority of patients may go unrecognized or not seek treatment, PPD can be treated successfully with an SSRI or an SNRI.[36,37] Prophylaxis for PPD may be recommended for women who have recurrent depression or experienced previous PPD.

Peri- and Postmenopausal Periods

As women transition into menopause, especially those with a previous history of depression, they are at increased risk of developing a recurrent episode.[12] Some studies indicate that estrogen has antidepressant effects, improving both depressive and physical symptoms, in perimenopausal women,[38] and preliminary evidence suggests that estrogen therapy improves both response and remission rates for SSRIs, but not for SNRI therapy.[39,40] However, estrogen as an adjunctive treatment for depression requires further study in peri-/postmenopausal women. Other preliminary evidence

Table 3

Gender Differences in Response to Treatment of Depression[14-17]

- Women may respond better to SSRIs and MAOIs than TCAs
- Women may respond more slowly to antidepressants than men
- Remission rates in both women and men may be higher with SNRIs than SSRIs
- Menopausal status may affect response to treatment
- Augmentation strategies may differ (eg, thyroid hormone, estrogen)
- Response to cognitive behavioral and interpersonal therapies is similar in women and men
- Combined psychotherapy and pharmacotherapy with TCAs is better than psychotherapy alone in men of all age groups and in women ≥50 years

MAOIs = monoamine oxidase inhibitors; SNRIs = serotonin-norepinephrine reuptake inhibitors; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

suggests that the SNRI venlafaxine may be more effective for achieving remission in postmenopausal women than SSRIs, which is similar to findings in younger women.[40] Although younger women appear to respond better to SSRIs than to TCAs, response rates to these antidepressant classes are similar in postmenopausal women.[14]

Findings from the Women's Health Initiative (WHI) that the health risks of hormone therapy may outweigh its benefits suggest that decisions regarding its use be based on risk/benefit assessments.[41] Because many peri-/postmenopausal women have discontinued hormone therapy abruptly and because fewer women will now begin this therapy, primary care physicians may see an increase in the number of women with depression, particularly women with mild depression. Therefore, an increased level of vigilance is warranted to detect the signs and symptoms of depression and to initiate appropriate treatment.

DIAGNOSIS AND COMORBIDITIES OF DEPRESSION

"Depression is frequently comorbid with many common medical conditions; accurate diagnosis and treatment of depression in these patients may have a significant beneficial effect on the course of the primary medical condition."
S.P. Roose, MD

As a common comorbidity with medical conditions such as cardiovascular disease (CVD) and chronic pain, depression can have a deleterious impact on prognosis. A common misconception is that CVD is a leading cause of death in men only. In fact, more women than men die of CVD annually (505,661 vs 440,175), and women's death rate from CVD is more than 10 times that from breast cancer. Moreover, mortality within 1 year after an initial myocardial infarction (MI) is higher in women than men (38% vs 25%).[42]

Depression and Cardiovascular Disease

The estimated prevalence of significant depressive symptoms post-MI is 45%, while major depression occurs in approximately 15% to 22%. Depression is an important independent risk factor for the occurrence of major cardiac events, and it is an independent risk factor for death following MI. This is supported by a prospective study that examined the impact of depression on 6-month survival. The results showed that depression was a significant predictor of mortality. Patients who were post-MI, had ventricular premature contractions post-MI, had unstable angina, or had severe heart failure experienced a much lower survival rate if they also had depressive symptoms versus the ones who did not.[43] Several potential mechanisms for increased CVD risk in depression have been suggested: increased risk of arrhythmias/sudden cardiac death, increased platelet aggregation, possible alterations in lipid metabolism, decreased adherence to lifestyle changes (depressed patients are less likely to adhere to exercise programs or to quit smoking), and decreased adherence to treatment regimens, including low-dose aspirin.[44-46]

Treating depression in patients with CVD may either increase or decrease CVD risk. Antidepressant drugs have multiple mechanisms of action that impact not only the central nervous system but also other body systems. Two important considerations in patients with CVD are heart rate variability and platelet activation. Reduced heart rate variability, an indicator of vulnerability to developing arrhythmias and of mortality, has been documented in patients with depression.[47] Heart rate variability is further decreased by TCAs, thus increasing CVD risk in already high-risk patients, whereas SSRIs improve heart rate variability. TCAs also have been shown to promote platelet aggregation, increasing the risk of thrombosis.[48]

Depression and Chronic Pain

Somatic complaints are now recognized as symptoms of depression in late life, suggesting a need for age-adjusted criteria for depression. In the population older than 60 years, 18% take analgesic medication on a regular basis, and of these, 63% take prescription pain medications for more than 6 months.[49] Pain in this population is underdiagnosed and undertreated, in part due to such common misperceptions that pain decreases with age or is a normal part of aging and due to the stigma attached to having chronic pain. A large study found that the prevalence of chronic painful conditions increased dramatically with age and was higher across all age groups in women than in men.[50] There also was a correlation between the number of depressive symptoms and the rate of chronic pain conditions: two depressive symptoms were associated with a 29% rate of pain conditions, compared with a rate of 62% for eight symptoms. Despite these strong associations, pain is not a criterion for major depression (Table 4),[6] perhaps because the pain–depression interaction is not completely understood.

The efficacy of antidepressants for treating chronic pain varies by class. Considerable evidence indicates that TCAs are effective for

Table 4

Criteria for Major Depression[6]

- Depressed mood
- Markedly diminished interest or pleasure
- Significant weight loss or weight gain
- Insomnia or hypersomnia
- Psychomotor agitation or retardation
- Fatigue or loss of energy
- Feelings of worthlessness or excessive or inappropriate guilt
- Diminished ability to think or concentrate, or indecisiveness
- Recurrent thoughts of death

psychogenic pain and peripheral neuropathies. Their analgesic effect is not due to an antidepressant effect in that there is no relationship between pain relief and TCA blood levels and they are effective even in the absence of depression.[51,52] However, SSRIs generally are not effective for treating chronic pain,[52] and the SNRI venlafaxine is effective only at doses above 150 mg.[53]

Diagnosis of Depression

"A yes to either or both of the following questions is a good positive screen for depression:

- **In the last month, have you lost pleasure in the activities you normally enjoy?**
- **In the last month, have you felt sad, down, depressed, or hopeless?"**

J.A. Lieberman III, MD, MPH

Although primary care physicians are expected to recognize both general medical and mental health concerns in their patients, recognition of psychiatric problems is low due to the limited time spent with a patient at each visit, unfavorable reimbursement rates, and the stigma for patients that is associated with a diagnosis of a mental disorder.[54] There are easy and quick techniques to facilitate recognition of mental health problems. One is the BATHE interviewing paradigm as part of the problem-oriented medical record procedure (Table 5).[54-56] A positive screen for depression is a yes to either or both of the following questions: In the last month, have you lost pleasure in the activities you normally enjoy? In the last month, have you felt sad, down, depressed, or hopeless? The SIG E CAPS system (Figure 1) is useful for quantifying which of the diagnostic symptoms for depression the patient is experiencing.[54] A positive response to five of the eight symptoms including depressed mood or anhedonia correlates with a diagnosis of depression.

ACHIEVING REMISSION—A MODEL OF EFFICACY

"Treating to remission, ie, achieving a virtually asymptomatic state, rather than response is the ultimate goal of antidepressant therapy."
M.H. Trivedi, MD

Remission of depression—no symptoms and return to full functioning in all areas of life—as a goal of treatment has not been evaluated in most randomized clinical treatment trials conducted to date. The shift in the treatment paradigm for depression from one of alleviation of symptoms or response to treatment to one of sustained remission requires a redefinition of long-term treatment goals and a reassessment of how to evaluate ongoing treatment for symptom relief after the usual 8- to 12-week treatment period of clinical trials. Not treating to remission increases the economic burden of depression due to a higher risk of relapse,[10,57-60] more rapid relapse, increased rate of recurrence, and increased risk of suicide,[60] as well as shorter well intervals and fewer symptom-free weeks.[57]

Table 5

The BATHE Technique[55]

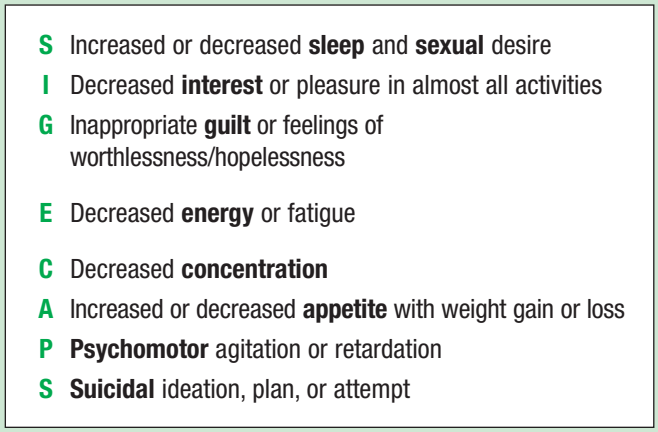
• **B**ackground	"What is going on in your life?"
• **A**ffect/feeling	"How are you feeling about that?"
• **T**rouble	"What troubles you most?"
• **H**andling	"How are you handling that?"
• **E**mpathy	"That must be very difficult."

"Three factors that commonly contribute to poor treatment outcomes are an inadequate treatment trial with a particular agent, use of a suboptimal dose, and lack of monitoring for symptomatic and functional improvement."
M.H. Trivedi, MD

Strategies to achieve remission are summarized by phase of treatment in Table 6.[61] In the selection of an antidepressant agent, factors to consider for improving outcome are previous history of response, which is a potent predictor of outcome, using an agent that affects multiple neurotransmitter systems, and gender differences in response. Three factors that commonly contribute to poor treatment outcomes in depression are inadequate length of treatment with a particular agent, use of a suboptimal dose, and lack of monitoring for symptomatic and functional improvement. Recent studies question the common perception of the necessity for changing treatment if significant improvement is not achieved in 4 to 6 weeks.[62,63] In one study, the remission rate increased from 32% at 6 weeks to 52% at 12 weeks,[62] while in another, approximately 40% of patients who

Figure 1

SIG E CAPS System[54]



Adapted with permission from Lieberman JA III. Depression: a common illness uncommonly diagnosed. *Psychiatric Ann*. 2002;32:522-526.

Table 6

Phases of Treatment

Treatment Phase	Goal
• Acute	Symptomatic remission Resolve tactical issues (eg, dosing, compliance)
• Continuation	Recovery from episode Restore psychosocial functioning (follows symptomatic remission by 1 to 3 months) Reduce likelihood of relapse
• Maintenance	Required for most patients Prevent recurrence

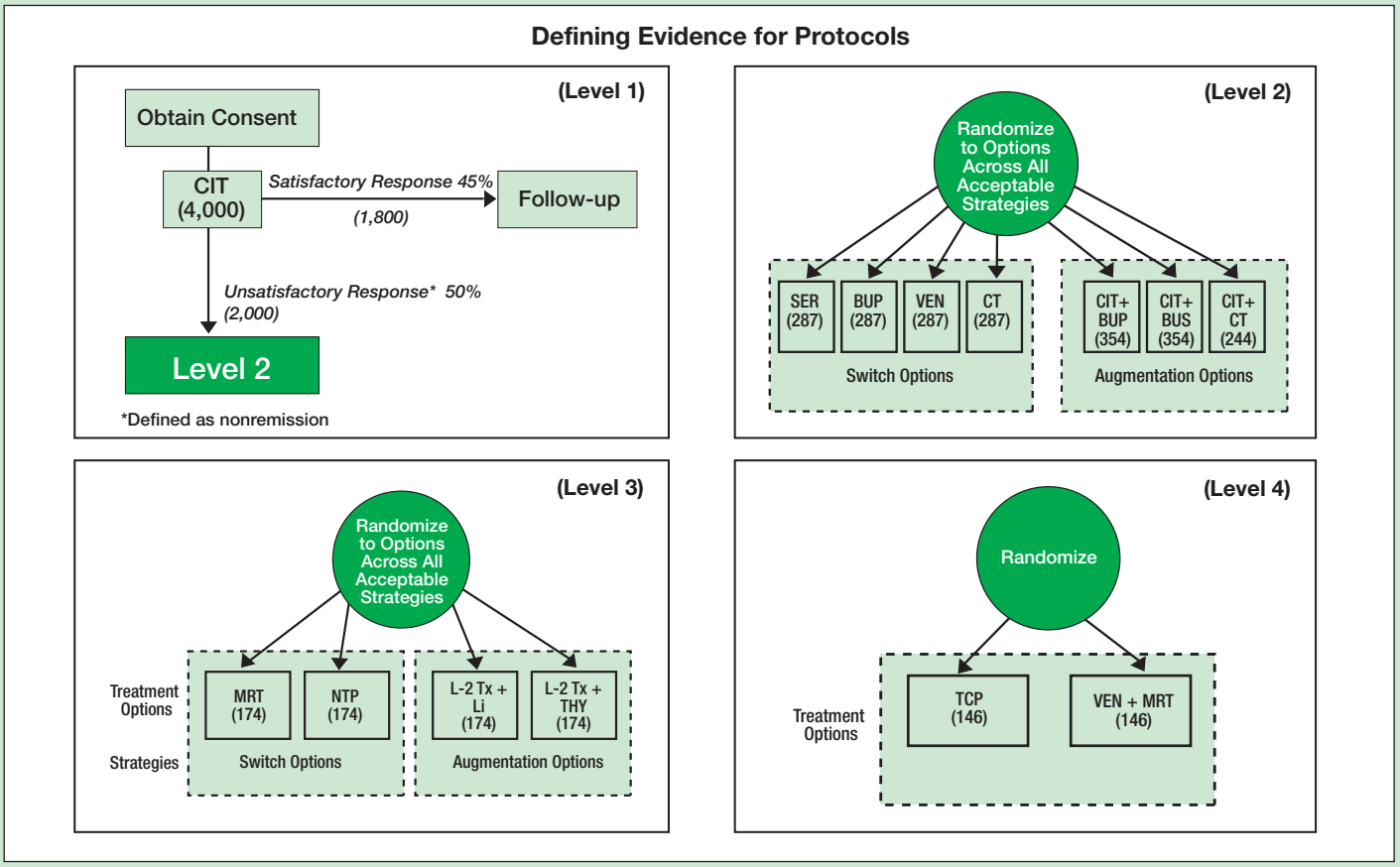
showed response during a 12-week acute-phase trial went on to achieve full remission with an additional 16 weeks of treatment.[63] Frequent monitoring of symptom relief and treating with the maximum tolerated dose, not the minimum dose to relieve symptoms, are two key strategies to optimize treatment outcomes.

By definition, evaluations of response necessitate the use of an objective assessment scale.[64] Such scales are commonly used in treatment trials, but they may be too cumbersome for routine use in clinical practice. In addition, while a threshold score may be used to evaluate remission (eg, ≤7 on the HAM-D scale),[65] the relevant definition of remission in clinical practice is the patient's return to full functioning. Global improvement scales, while simpler, do not provide an accurate assessment of the patient's level of improvement with treatment. The SIG E CAPS system, which includes all of the core symptoms for depression (Figure 1),[54] and the self-administered Patient Health Questionnaire depression module (PHQ-9)[66] are useful tools for assessing improvement, although they have not been studied with respect to monitoring outcome over time. Although there is no single instrument to monitor therapy that serves everyone's needs optimally, the use of any generally accepted assessment tool will provide a basis to measure the result of therapy.

The ongoing Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial of the National Institute of Mental Health of the National Institutes of Health provides a model for developing

Figure 2

Strategies for Treating Depression to Remission: The STAR*D Trial



BUP = bupropion; BUS = buspirone; CIT = citalopram; CT = cognitive therapy; L = level of protocol; Li = lithium; MRT = mirtazapine; NTP = nortriptyline; SER = sertraline; TCP = tranylcypromine; THY = thyroid hormone; Tx = treatment; VEN = venlafaxine.

guidelines/algorithms that can be used by physicians at critical points of care to determine whether to continue treatment, increase the dose, or change the therapeutic strategy in order to achieve remission. The primary care (40%) and specialty (60%) sites participating in the study are clinical practice settings, not research sites. Patients initially receive an SSRI for up to 12 weeks; those not achieving remission are randomized in the second phase of the trial to augmentation strategies (ie, addition of a second antidepressant or cognitive therapy) or to switch options (ie, different antidepressant or cognitive therapy). There are four phases of randomized treatment for patients not achieving remission after 12 weeks in any phase (Figure 2, page 7). Decisions regarding next steps are made according to time- and improvement-based critical decision points determined at each visit (initial, weeks 4, 6, 9, and 12) using a 16-item rating scale of the nine core symptoms for depression and a side-effect burden score. The STAR*D trial design underscores the importance of frequent patient follow-up visits once therapy is initiated to monitor outcomes and to ensure that patients have an adequate therapeutic trial on a particular antidepressant before an addition or switch in therapy is made.

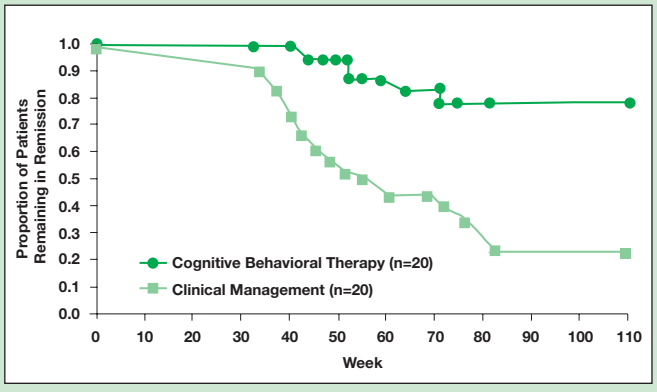
The addition of depression-targeted psychotherapies may be necessary in some patients. Psychotherapy interventions may be successful in patients who have failed antidepressant treatment trials. In addition, cognitive behavioral therapy added to successful antidepressant treatment sustains remission (Figure 3) and prevents relapse.[67,68] Cognitive behavioral therapy also prolongs the time to relapse in successfully treated patients with residual symptoms, which are more common in severely ill patients and are a strong predictor of early relapse.[58,67,68]

TREATMENT STRATEGIES

Treatment of depression in controlled clinical trials is relatively successful. Up to 60% of patients respond to medication, psychotherapy, or a combination of the two treatments. However, 29% to 46% of patients fail to respond fully to what could be considered adequate antidepressant therapy.[69] Of note is that patients included in controlled clinical trials are not reflective of patients typically treated by primary care physicians; that is, they typically do not have comorbid conditions, such as anxiety disorders and substance abuse, or concomitant general medical conditions. Successful treatment of depression, like other medical illnesses, requires a systematic approach in which patients are assessed frequently for response to the prescribed treatment and adjustments in therapy are made based on the assessments (Figure 4).[4]

Figure 3

Depressed Patients Remaining in Remission 2 Years After Cognitive Behavioral Therapy or Clinical Management[67]



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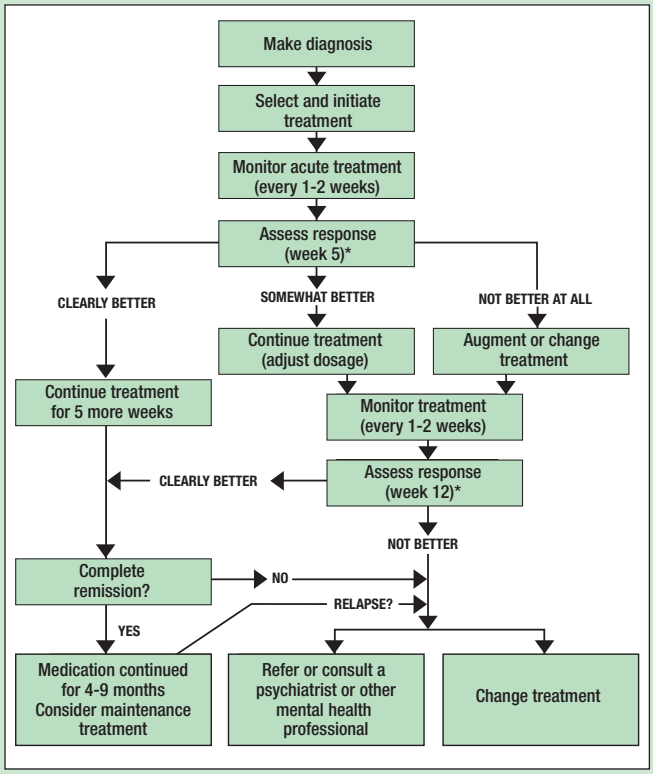
"Scales are [sometimes] tough to use in the real world. Focus on improvement in the patient's target symptoms to guide treatment."
R.R. Krishnan, MD

What treatment strategies can be used to successfully treat patients with depression to remission? First, it is important for the physician and patient to establish a partnership by setting the goals of

Figure 4

Overview of Treatment of Depression



*Times of assessment (weeks 6 and 12) rest on very modest data. It may be necessary to revise the treatment plan earlier for patients failing to respond at all. Reprinted with permission from the Depression Guideline Panel. *Depression in Primary Care, Volume 2: Treatment of Major Depression.* Clinical Practice Guideline Number 5. Rockville, Md:US Dept of Health and Human Services, Public Health Service, Agency for Health Care Policy and Research; 1993. AHCPR Publication 93-0551.

Table 7

General Principles of Treatment

- Form partnership with patient
  - Set goals of treatment
  - Educate patients regarding need for long-term treatment
- Select medication and dosage
  - High long-term tolerability
  - High safety in overdose
- Medication fails to achieve remission or side effects intolerable
  - Consider switch within or to another class or augmentation strategies
  - Consider switch to newer options
- Provide psychotherapy
  - Medication adherence
  - Early detection of recurrence, residual symptoms
  - Identification of axis II disorders
  - Psychosocial issues
- Measure symptomatic and functional outcomes

treatment together and for the physician to ensure that the patient understands that remission of depression is an achievable goal. Second, it is important to recognize the three phases of treatment—acute, continuation, maintenance—and the goals of each phase (Table 6). Remission of symptoms and a good prognosis long term are the ultimate goals of all phases of treatment. Maintenance treatment, which is necessary for most patients, generally requires convincing patients to remain on therapy and is analogous to long-term therapy for cholesterol lowering or control of blood pressure. Third, the general principles of treatment summarized in Table 7 and the schematic of strategies for treatment in Figure 2 provide a helpful framework for initiating and continuing or switching treatments. Focusing on target symptoms for a particular patient is the best way to guide treatment in clinical practice settings. Psychotherapy and newer options (eg, "modern" electroconvulsive therapy, transcranial magnetic stimulation, and vagal nerve stimulation) are performed outside the primary care setting and necessitate a multidisciplinary approach, as discussed in the next section.

Table 8

Strategies to Achieve Remission[61]

- Selection of antidepressant (maximize benefits using agents with multiple neurotransmitter effects; prior history of response)
- Maximize antidepressant dose and duration of treatment (higher dose, longer trial)
- Monitor outcomes frequently to optimize treatment
- Augmentation strategies (use of another pharmacologic agent to enhance antidepressant effect)
- Switch to another antidepressant if necessary
- Combination antidepressants (concomitant use of ≥2 antidepressants to achieve effect)
- Antidepressants + psychotherapy

Important in the application of the general principles of treatment (Table 7) and the strategies to achieve remission (Table 8) is the recognition that patients who experience remission of their depression are less likely to relapse than are patients who respond but have residual symptoms.[70] Those with remission of symptoms by 3 months are one third less likely to have a relapse/recurrence of depression long term.[71] Independent of treatment approaches, patients with depression of >52 weeks' duration have a lower probability of achieving remission.[69,72] Thus, early and effective treatment is necessary to avoid chronicity of depression.

Treatment Interventions

The six major classes of antidepressants affect monoamine oxidases that regulate brain systems. They inhibit serotonin, norepinephrine, and/or dopamine; some are mixed action drugs, and some are MAOIs. While there are many agents within the classes of antidepressants, no one drug fits most patients even half of the time. Initial medical treatments usually produce a response in 50% to 60% of patients, while remission rates are lower.[73] Thus, changes in or additions to therapy are common when treating patients with depression. Nonetheless, consideration of several factors when selecting an antidepressant may help optimize initial therapy (Table 9). In addition, characteristics of the various antidepressant classes that aid in the selection of therapy for a particular patient are summarized in Table 10 (page 10) and Figure 5 (page 11).[4,73-84]

Table 9

Factors Affecting Medication Selection

- Prior positive response to an agent
- History of nonresponse to a specific agent
- History of intolerance to a specific agent
- Pretreatment symptom features (eg, atypical or psychotic)
- Response to an agent in first-degree relative(s)
- Severity of associated symptoms (eg, anxiety, insomnia) not predictive of response
- Side effects beneficial in short term are possible liabilities in long term (eg, sedation)

Even within a class, such as the TCAs, heterogeneous effects on neurotransmitter systems are evident. For example, nortriptyline and maprotiline are substantially more selective for norepinephrine than for serotonin, whereas amitriptyline and imipramine have nearly equal selectivity for both neurotransmitters.[85] As suggested by the data listed in Table 10 for the various antidepressant classes, those that activate more than one neurotransmitter system (eg, the SNRIs) produce higher rates of remission for depression compared with those that act selectively on one neurotransmitter (eg, SSRIs). A meta-analysis of efficacy data from 102 randomized controlled trials and tolerability data from 95 studies indicated that while SSRIs are better tolerated, TCAs with a dual mechanism of action are more effective than SSRIs.[86] Specifically, remission rates of 46% to 60% were reported for TCAs with a dual mechanism compared with rates of 19% to 30% for SSRIs.[85] The SNRI venlafaxine also has shown significantly greater remission rates compared with SSRIs.[18,73,85,87] A meta-analysis of eight comparative studies demonstrated remission rates of 45% for the SNRI, 35% for SSRIs, and 25% for placebo, with a significant difference noted at week 2 in favor of the SNRI.[87] In addition, SNRI remission rates of 40% to 55% at week 8 were significantly superior to rates of 31% to 37% for SSRIs regardless of age or gender.[18]

Selecting an antidepressant with a low incidence of long-term side effects enhances adherence to treatment, especially long term. Once remission is achieved, the antidepressant should be continued at the same dosage for the continuation and maintenance phases of treatment to prevent relapse and/or recurrence. Sometimes, it may be

Table 10

Comparison of Major Antidepressant Classes[4,74-84]

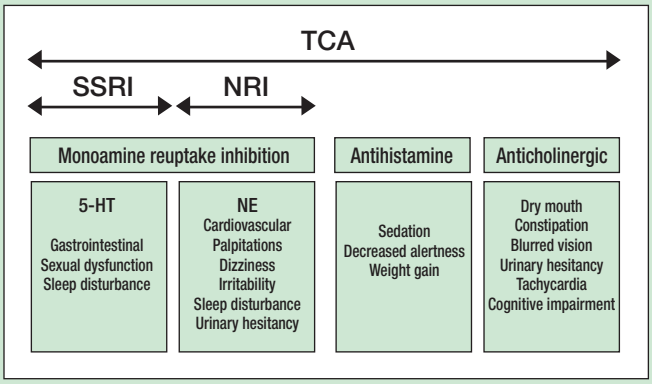
Antidepressant Class	Mechanism of Action	Response and Remission Rates*	Other Characteristics
MAOIs, older (phenelzine, tranylcypromine)	Irreversible inhibition of MAO-A and MAO-B; Enhance NE, 5-HT, DA	60%-70%	May be better in atypical depression Require dietary restrictions
TCAs (amitriptyline, amoxapine, desipramine, doxepin, imipramine, nortriptyline, protriptyline, trimipramine)	Block reuptake of NE, 5-HT	43%-70%† 25%-60%†	Analgesic, anticholinergic, and antimuscarinic actions High side-effect burden
Tetracyclic (maprotiline)	Block reuptake of NE	53%-63%	Similar to TCAs Risk of seizures at higher doses
SSRIs (fluoxetine, sertraline, paroxetine, citalopram, escitalopram, fluvoxamine)	Selectively block reuptake of 5-HT	60%-70% 20%-35%	Broad comorbidity coverage Less side-effect burden vs TCAs Safe in overdose
SNRI (venlafaxine)	Block reuptake of 5-HT and NE	65%-76% 37%-45%	Higher remission rates Less side-effect burden vs TCAs Safe in overdose
NDRI (bupropion)	Block reuptake of NE and DA (?)	52%-70%	Effective for smoking cessation Less sexual dysfunction Safe in overdose
SA (mirtazapine)	Potent antagonist of 5-HT_2, 5-HT_3, and H_1 receptors; moderate α_1-adrenergic antagonist; moderate antagonist at muscarinic receptors	70%	Safe in overdose Common TCA and SSRI side effects minimized Sedation, weight gain
SA/SRI (nefazodone)	Antagonist of 5-HT_2 receptors and blocks reuptake of 5-HT and NE	35%-67% 35%-52%	Modest antidepressant Used mainly for hypnotic and anxiolytic effects

* Commonly accepted definitions: response = ≥50% reduction in the Hamilton Rating Scale for Depression (HAM-D) or Montgomery-Asberg Depression Rating Scale (MADRS) score; remission = absolute score of ≤7 on the HAM-D-17 or absolute score of ≤10 on the HAM-D-21 scales.

† Variability in response and remission rates due to heterogeneous selectivity on norepinephrine and serotonin within the class; higher rates associated with agents that have an approximately equal effect on both neurotransmitters. DA = dopamine; 5-HT = serotonin; MAOIs = monoamine oxidase inhibitors; NDRI = norepinephrine–dopamine reuptake inhibitor; NE = norepinephrine; SA = serotonin antagonist; SA/SRI = serotonin antagonist/serotonin reuptake inhibitor; SNRI = serotonin–norepinephrine (noradrenergic) reuptake inhibitor; SSRIs = selective serotonin reuptake inhibitors; TCAs = tricyclic antidepressants.

Figure 5

Adverse Consequences of Current Antidepressant Therapies[76]



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necessary to adjust the dose to maintain response and tolerability in the continuation and maintenance phases. Patient education regarding the long-term course of depression and its treatment is important for promoting adherence to the medication regimen.

Maintenance therapy is essential for patients with recurrent episodes of depression. For these patients, depression as an illness is analogous to other chronic medical illnesses (eg, hypertension, diabetes) and may require lifelong therapy with periodic assessments at 3- to 6-month intervals after remission is achieved. The goal is to restore and maintain a normal level of functioning with minimal symptoms longterm. For successful treatment of their patients, primary care physicians need to be attuned to any variability in mood and symptomatology after patients have been in remission.

Psychotherapy combined with antidepressant medication is indicated for patients with severe, recurrent, complex, or chronic depression. It also is indicated for patients in whom there is only a partial response of symptoms or an incomplete restoration of psychosocial functioning. Psychotherapy is useful for getting patients to maintain adherence to their medication regimen long term in order sustain remission. Other objectives of psychotherapy are to prevent relapse/recurrence and improve psychosocial function.

When should a primary care physician refer a patient to a mental health specialist for treatment? At the time of the initial diagnosis of depression, complicating disorders such as severe anxiety or substance abuse or a diagnosis of bipolar disorder would prompt a referral for treatment. The need for addition of psychotherapy may prompt a referral. For other patients, the answer, in part, is the comfort level of the physician and patient with treatment and its progress. Referral for a second opinion is indicated if a patient has not achieved remission after two adequate treatment trials in 6 months.

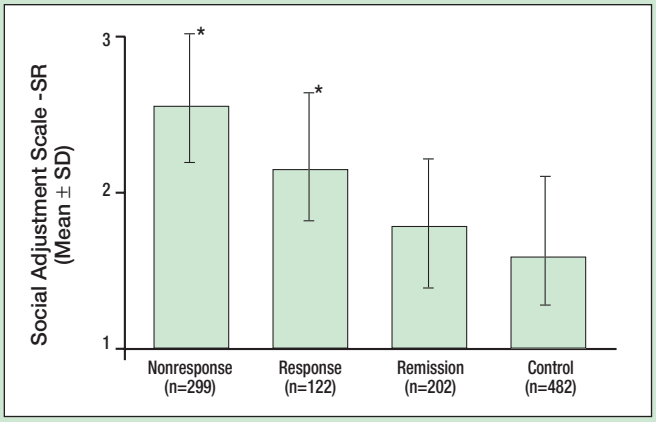
MULTIDISCIPLINARY APPROACH TO TREATMENT

The purpose of using a multidisciplinary approach to the treatment of depression is to maximize the patient's chances of achieving remission, particularly early remission, which predicts better outcomes and long-term success.[58,71,88] Patients who achieve remission are nearly equivalent to a normal control population with respect to quality-of-life factors (Figure 6).[88]

The approach to treatment shown schematically in Figure 4 allows for different levels of intervention and a multidisciplinary approach to treatment. Studies have shown that outcomes improve when there is active collaborative intervention as well as medical treatment.[89-91] In one study of intensive treatment (frequent visits to primary care physicians and psychiatrists, monitoring for medication adherence, and patient education), medication adherence at 90 days was approximately 33% higher and response rates 40% higher with intensive treatment versus usual care.[91] A 2-year quality improvement study conducted in primary care practices in managed care groups utilized depression nurse specialists for 6 to 12 months in the quality improvement medication and therapy groups for patient screening, assessment, and education according to the Agency for Health Care Policy and Research (AHCPR) guidelines,[3,4] while the usual care group providers received only the guidelines. The medication and therapy groups had better adherence to medication regimens, even in patients at high risk for relapse, out to 18 months compared with usual care.[90] In a third study of patients who were symptomatic after 6 to 8 weeks of antidepressant therapy, approximately twice as many of those randomized to collaborative care were asymptomatic at 3 months compared with those who continued usual care.[91] Similar to the STAR*D study, a successful stepped collaborative care approach assesses patient outcomes at defined points, with the intensity of care increased in those patients who have not met the defined endpoint.

Figure 6

Impairment in Work, Relationships, and Quality of Life[88]



*$P \leq 0.05$ compared with the remission group.

"In the absence of an ongoing collaborative relationship with the patient, all of the multidisciplinary intervention in the world is probably going to be essentially useless."
J.E. Kelsey, MD, PhD

Defining roles in multidisciplinary treatment teams is an intellectual exercise since most healthcare practitioners can assume the various responsibilities involved in screening, diagnosis, education, assigning care, assessment, and evaluation of response to treatment. For multidisciplinary interventions to be successful, there must be an ongoing collaborative relationship with the patient; that is, the patient must be an active member of the team. It also is important for the approach to be integrated among the disciplines to avoid the patient's time and care being overly fragmented. The biopsychosocial model of treatment utilized in a multidisciplinary team approach that actively includes patients increases the likelihood that patients will achieve remission of their depression long term, thereby improving outcomes.

FUTURE DIRECTIONS IN THE MANAGEMENT OF DEPRESSION

Although often considered an episodic illness by primary care physicians, depression actually is a chronic debilitating illness that, if left untreated, can significantly increase the risk of suicide.[3] The approach to treatment, therefore, is analogous to other chronic diseases (eg, diabetes, hypertension, hypercholesterolemia) treated by primary care physicians, ie, long-term treatment. The goals of treatment are for patients to have an absence of symptoms and a level of psychosocial functioning similar to that in normal individuals and to prevent relapse or recurrence of depression. The importance of remission as the goal of treatment of depression is well established in the psychiatric literature. Remission is associated with a better prognosis and outcomes. Clinical treatment trials have used discriminators and recognized validated scales to assess remission. However, such measures generally are not practical for use in clinical practice sites.

Primary care physicians are called on increasingly to serve as the primary mental health provider for women and men in the United States. Yet, it is unclear how to determine remission of depression in their patients. Just as there are guidelines for treating other chronic medical illness, there is a need to develop treatment guidelines/algorithms and assessment instruments for depression that are easily used in clinical practice settings at the point of care. Treating to remission requires higher levels of response to treatment based on widely used objective assessment scales. The ongoing STAR*D trial is a useful model for developing treatment guidelines/algorithms for use at critical decision points of care.

Future directions include additional studies conducted in clinical practice sites with remission of depression as a primary endpoint and evaluation of simple, quick instruments to reliably assess remission. Such studies will serve as the basis for developing treatment guidelines/algorithms for the treatment of depression to remission by primary care physicians. Understanding and application of the concepts of treating depression as a chronic illness and to complete resolution of symptoms by primary care physicians fulfills their ultimate goal in providing care—improved treatment outcomes in patients with depression.

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ACHIEVING REMISSION IN DEPRESSION: Managing Women and Men in the Primary Care Setting

Post-test

Instructions for Continuing Education Credit

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Release Date: September 2003
Expiration Date: September 30, 2004

1. All of the following statements regarding gender differences are true, except:
   a. The prevalence of major depression in women is approximately twice that in men.
   b. Women with depression are more likely to have eating disorders and shorter episodes of depression compared with men with depression.
   c. Women tend to respond better to selective serotonin reuptake inhibitors than to tricyclics.
   d. Gender differences regarding the evaluation and treatment of depression are preliminary and based on post hoc analyses of study data.

2. All of the following statements are true, except:
   a. The strongest predictor of postpartum depression is depression prior to or during pregnancy.
   b. Women with moderate to severe symptoms of premenstrual anxiety and irritability have levels of impairment nearly comparable to those observed in major depression.
   c. The risk of prenatal exposure to antidepressants never outweighs their benefit in women with depression.
   d. Estrogen therapy may improve response to selective serotonin reuptake inhibitors in postmenopausal women.

3. Which of the following statements is true regarding depression?
   a. Depression is frequently comorbid with general medical conditions and can adversely affect prognosis.
   b. Treatment for depression is unsuccessful in 80% or more of patients.
   c. Depression is an episodic condition that requires only short-term therapy.
   d. There is no association between depressive symptoms and chronic pain conditions.

4. All of the following are diagnostic criteria for depression, except:
   a. Insomnia
   b. Fatigue
   c. Pain
   d. Diminished ability to concentrate

5. Which of the following is the goal of the treatment of depression?
   a. Symptom relief
   b. Response
   c. Relapse
   d. Remission

6. All of the following are principles for treating depression, except:
   a. Select an antidepressant agent that is safe in overdose.
   b. Use the lowest possible dose that relieves symptoms rather than the dose that achieves remission.
   c. Select an antidepressant agent with high long-term tolerability.
   d. If patients do not respond to an adequate treatment trial, therapy may be switched to another agent.

7. All of the following are factors for selecting an antidepressant drug for a particular patient, except:
   a. Severity of associated symptoms (eg, insomnia)
   b. Prior response to an agent
   c. Pretreatment symptom features (eg, atypical, psychotic)
   d. Response to an agent in a first-degree relative

8. All of the following are true regarding remission, except:
   a. Remission is defined as the absence of symptoms.
   b. Patients treated to remission are less likely to have a relapse or recurrence of their depression.
   c. Remission is defined as a level of psychosocial functioning similar to that in normal individuals.
   d. Once a patient reaches remission, antidepressant treatment can be stopped.

9. Which of the following mechanisms of action of antidepressant agents is more likely to produce remission of depression?
   a. Selectivity for the neurotransmitter serotonin
   b. Selectivity for the neurotransmitter norepinephrine
   c. Selectivity for the neurotransmitter dopamine
   d. Selectivity for both norepinephrine and serotonin

10. All of the following are true regarding psychotherapies, except:
    a. They can improve patient adherence to medication.
    b. They may be successful in patients who have failed medical treatment trials.
    c. They are not effective in patients with residual depressive symptoms.
    d. In conjunction with antidepressant treatment, they help sustain remission and prevent relapse of depression.

ACHIEVING REMISSION IN DEPRESSION: Managing Women and Men in the Primary Care Setting

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